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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/304,859	05/04/99	BERD	D 1225/1E251-U

EXAMINER

HM12/0814

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ART UNIT	PAPER NUMBER
1642	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Application No.	Applicant(s)
09/304,859	Berd, David
Examiner	**Art Unit**
Jennifer Hunt	1642

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 15, 2001* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-10 and 12-24* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-10 and 12-24* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *18*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Continued Prosecution Application

1. The request filed on 6/12/2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/304,859 is acceptable and a CPA has been established. An action on the CPA follows.

2. Acknowledgment is made of applicant's cancellation of claim 11, and addition of new claim 24. Claims 1-10 and 12-24 are pending in the application and under consideration.

Claim Rejections Maintained/New Grounds of Rejection

3. Claims 1-10 and 12-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of Bed (US #5,290,551), in view of Elliot et al. (US #5,478,556), or Mankiewicz et al., Cancer Immunol. Immunother., Vol. 2, pages 27-39, 1977, or Humphrey et al., Surgery, Gynecology, and Obstetrics, pages 437-442, March 1971. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 1 of US #5,290,551 recites a vaccine composition which is a tumor cell extract wherein the tumor cells are melanoma cells. The extract is conjugated to a hapten, the same tumor type as the patient's tumor, not allogenic to said patient and incapable of growing in the

patient's body after injection. Claim 2 of '551 recites a method of treating melanoma comprising administering cyclophosphamide, followed by a therapeutically effective amount of the vaccine of claim 1. The disclosure teaches a therapeutically effective amount that includes administration of the vaccine more than 6 times (column 4, line 65-66 and column 5, line 1-11), administration of a 300mg/M^2 dose of cyclophosphamide prior to vaccination (column 4, line 60), a dosage of tumor cells including 10 X 10^6 cells, which is at least 10^6 tumor cells per dose. (column 3, line 37), vaccination protocols which sensitize patient to the hapten prior to vaccination (column 5, line 52), vaccination protocols which do not sensitize patient to the hapten prior to vaccination (column 4, example 1) and that the effective amount is indicated by infiltration of the tumor by activated T lymphocytes (column 3, line 67-68). All of the treatments are administered to human patients.

With regard to claims 9-10 and 20-21 of applicant's invention, claim 1 of '551 specifically recites use of a hapten selected from the group comprising dinitrophenyl....etc.

With regard to claims 12 and 22-24 of applicant's invention, claim 1 of '551 specifically recites administration with an adjuvant, wherein the adjuvant is *Bacille Calmette-Guerin.*

Berd US #5,290,551 fails to teach weekly injections or administration of cyclophosphamide (CY) only prior to the first dose of the vaccine.

Vaccination protocols comprising weekly booster injections of inactivated autologous tumor cell extract, and administration of cyclophosphamide prior to the first injection is known in the art.

See for example, Elliot (US # 5,478,556), which at column 4 describes administration of an autologous tumor vaccine with prior administration of cyclophosphamide (CY), and weekly vaccine administration protocol, column 4, lines 20-25.

See also for example, Mankiewicz et al., which at page 28, column 2, describes administration of an autologous tumor vaccine with weekly vaccine administration protocol.

See also for example, Humphrey et al., which at page 437, column 2, describes administration of an autologous tumor vaccine with weekly vaccine administration protocol.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer weekly injections of the composition disclosed in Berd US #5,290,551, and to administer cyclophosphamide prior to the first injection for the purpose of optimizing the claimed "therapeutically effective amount", because weekly boosters and administration of cyclophosphamide prior to the first injection were well known vaccine protocols, as exemplified in Elliot et al., Mankiewicz et al., and Humphrey et al.

Therefore the instant claims 1-10 and 12-24 are obvious over claims 1-2 of US 5,290,551 and thus are rejected under the judicially created doctrine of obviousness-type double patenting.

4. Claims 1-10 and 12-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berd (US# 5,290,551), or Berd et al., Cancer Research, Vol. 51, pages 2731-2734, May 15, 1991, or Berd et al., Proceedings of the American Association for Cancer Research, Vol. 35, pages 667-678, March 1994, in view of Elliot et al. (US #5, 478, 556), or Mankiewicz et al., Cancer

Immunol. Immunother., Vol. 2, pages 27-39, 1977, or Humphrey et al., Surgery, Gynecology, and Obstetrics, pages 437-442, March 1971.

'551 teaches a vaccine composition and method of inducing an anti-tumor response comprising administering the composition, in which the composition is a tumor cell extract wherein the tumor cells are melanoma cells. The tumor cell extract is conjugated to a hapten, the same tumor type as the patient's tumor, not allogenic to said patient and incapable of growing in patient's body after injection. This composition was administered more than 6 times. (col 4, lines 65-66 and col 5, lines 1-11) Prior to vaccination, patients were administered 300mg/M2 of cyclophosphamide. (Col 4, line 60) A dosage including 10 X 10^6 tumor cells was used, which is at least 10^6 tumor cells per dose. (column 3, line 37) The hapten is dinitrophenyl and is administered with the adjuvant Bacillus Calmette-Guerin. (col 5, lines 54-57) '551 teaches methods in which the patients is first sensitized to the hapten (col 5, line 52), and methods in which the patient is not first sensitized to the hapten. (col 4, example 1) The treatment is administered to human patients. The anti-tumor response induced is tumor infiltration by activated T lymphocytes. (Col 3, lines 67-68) '551 does not teach weekly administration of the composition, or administration of cyclophosphamide only prior to the first dose of the vaccine.

Berd et al., Cancer Research, teaches a composition and method of inducing an anti-tumor response comprising administering the composition, in which the composition is a tumor cell extract wherein the tumor cells are melanoma cells. The tumor cell extract is conjugated to a hapten, the same tumor type as the patient's tumor, not allogenic to said patient and incapable of

growing in patient's body after injection. This composition was administered more than 6 times. Prior to vaccination, patients were administered 300mg/M2 of cyclophosphamide. A dosage including 10 X 10^6 tumor cells was used, which is at least 10^6 tumor cells per dose. The hapten is dinitrophenyl and is administered with the adjuvant *Bacillus Calmette-Guerin*. Berd et al., Cancer Research, teaches methods in which the patients is first sensitized to the hapten. The treatment is administered to human patients. The anti-tumor response induced is tumor infiltration by activated T lymphocytes. (see for example, abstracts and Materials and Methods)

Berd et al., Proceedings of the American Association for Cancer Research teaches a composition and method of inducing an anti-tumor response comprising administering the composition, in which the composition is a tumor cell extract wherein the tumor cells are melanoma cells. The tumor cell extract is conjugated to a hapten, the same tumor type as the patient's tumor, not allogenic to said patient and incapable of growing in patient's body after injection. This composition was administered more than 6 times. Prior to vaccination, patients were administered 300mg/M2 of cyclophosphamide. The hapten is dinitrophenyl and is administered with the adjuvant *Bacillus Calmette-Guerin*. Berd et al., Proceedings of the American Association for Cancer Research, teaches methods in which the patients is first sensitized to the hapten, and methods in which the patient is not first sensitized to the hapten. The treatment is administered to human patients. The anti-tumor response induced is tumor infiltration by activated T lymphocytes.

Berd, US Patent #5,290,551, Berd et al., Cancer Research, and Berd et al., Proceedings of the American Association for Cancer Research, fail to teach weekly injections or administration of cyclophosphamide only prior to the first dose of the vaccine.

Vaccination protocols comprising weekly booster injections of inactivated autologous tumor cell extract, and administration of cyclophosphamide prior to the first injection is known in the art.

See for example, Elliot (US # 5,478,556), which at column 4 describes administration of an autologous tumor vaccine with prior administration of CY and weekly vaccine administration protocol, column 4, lines 20-25.

See also for example, Mankiewicz et al., which at page 28, column 2, describes administration of an autologous tumor vaccine with weekly vaccine administration protocol.

See also for example, Humphrey et al., which at page 437, column 2, describes administration of an autologous tumor vaccine with weekly vaccine administration protocol.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer weekly injection of the composition disclosed in Berd, and to administer cyclophosphamide prior to the first injection for the purpose of optimizing the "therapeutically effective amount", because weekly boosters and administration of cyclophosphamide prior to the first injection were well known vaccine protocols, as taught in Elliot et al., Mankiewicz et al., and Humphrey et al.

Arguments

The arguments presented by applicant simultaneously address both the double patenting and the 103 rejection and are twofold. First, applicant argues that the alteration of the method taught in Berd from the q28 day administration taught in Berd US #5,290,551 to the weekly administration instantly claimed is beyond the realm of "optimization" and constitutes a contribution beyond routine experimentation, because according to applicant, there is no motivation to modify the monthly vaccination administration regimen of Berd US #5,290,551 or Elliot US #5,478,556 because neither reference suggests that modifying either administration protocol would lead to optimization. Applicant further argues the references do not render the instant claims obvious because, applicant maintains, unexpected results are achieved when the vaccine taught in both the prior art and in the instant application is administered weekly, rather than monthly.

Applicant submits as support for these arguments (1) an example from the instant disclosure, (2) a declaration under rule 1.132 by Dr. Berd, which is supported by (3) post filing evidence. The arguments are as follows:

(1) With regard to the teachings in the instant specification, applicant points to Example 15, pages 52-53. In Example 15, 4 dosage regimens are described:

(A) Injection q 4 weeks X 8, with presensitization to hapten, yielding a 45% DTH response.

(B) Injection q week X 6, with presensitization to hapten, yielding a 11% DTH response.

(C) Injection q week X 12, with presensitization to hapten, yielding a 18% DTH response.

(D) Injection q week X 6, with no presensitization to hapten, yielding a 59% DTH response.

*It is noted by the examiner that the prior art indicates a nexus between DTH reaction and a tumor response/survival.

Applicant argues that "the data shows that weekly administration was clearly more effective than monthly administration".

(2) With regard to the declaration under 132, inventor Dr. David Berd explains that the 28 day vaccine regimen, taught in the prior art references (his own work) was selected to avoid administration of Cyclophosphamide (CY) more often than q28 days. Dr. Berd adds that weekly administration of the vaccine necessitates omission of cyclophosphamide prior to each treatment, and that the weekly protocols were modified to include administration of cyclophosphamide prior to the first vaccination, but not subsequently. Dr. Berd further explains that nothing in the prior art teaches or suggests that this agent (CY) could be omitted prior to each vaccination with improved results.

(3) The post filing evidence seeks to explain the results disclosed in the instant application, which indicate that some weekly vaccine regimens resulted in poor response, while others resulted in superior response compared to the q28 day regimen. In the abstract of Exhibit 2, it is described that the weekly regimen is most effective when an induction dose is administered at an appropriate time. The evidence cited is a comparative study of administration protocols, in

which patients which received a skin test 5-7 days prior to induction of therapy experienced greatly enhanced DTH response.

Applicant's arguments filed 6-12-2001 have been fully considered but they are not persuasive.

For the sake of clarity, first the method claims (1-10 and 12-17) will be addressed, and subsequently, the composition claims (18-24) will be addressed.

With regard to argument (1), the specification teaches four dosage regimens (A-D) in example 15, three of which (B-D) describe weekly vaccine administration. Of the three weekly protocols, two result in inferior immune stimulation, and one results in enhanced immune stimulation, when compared to q 28 day administration. The specification concludes thus that dosage may have significant influence on treatment efficacy, however this is a speculative conclusion, and the results set forth in the specification fail to provide the alleged unexpected equivalent or superior results when weekly vaccines are administered. These results constitute mere optimization of dosage regimens. Certainly, that the weekly administration of a vaccine produces equal or enhanced immune response compared to a q 28 day administration is not surprising. Further, two of the three weekly protocols resulted in vastly decreased response, when compared to the q 4 week regimen, and it is not clear from the specification as filed what difference between the vaccine protocols caused this large discrepancy.

As set forth previously, and expanded above, weekly vaccine protocols for cancer vaccines and immunotherapies were known in the art, and alteration to a weekly dosage regimen

would not constitute undue experimentation but rather simply optimization. The courts have held that "[Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40C and 80C and an acid concentration between 25 and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100C and an acid concentration of 10%.). Further, as set forth above, there is no clear evidence that the weekly administration of a vaccine results in overall increased efficacy. Although it is clear that the protocol of group D resulted in enhanced treatment, there is no evidence that this increased efficacy is a result of weekly vaccine administration. In fact, there is contrary evidence of such, since the weekly administrations to Groups B and C resulted in poor response. Further, the specification provides no guidance as to what the difference between the protocols of B and C to D was that resulted in the differences. It is not until after filing, with further experimentation that lead applicant to a very specific regimen that happened to produce enhanced results similar to those of Group D. This leads to applicants arguments (2) and (3).

With regard to argument (2), the rule 1.132 declaration, which points to a specific alteration of cyclophosphamide and vaccine administration change as critical to the unexpected results, is not commensurate in scope with the claims.

The claims are broadly drawn to any weekly protocol for vaccine administration, including different cyclophosphamide (CY) dosages and number of administrations, different adjuvants, etc. The protocol which achieved unexpected results, however, was far more specific, and it is clear that numerous weekly administrations do not include the same results (see Groups B and C from the instant specification, Example 15)

The declaration and post filing evidence clearly states that it is the single administration of cyclophosphamide administration, in combination with an induction dose of vaccine and then weekly vaccine administration which achieves unexpected results. Further, the evidence supplied by the post filing evidence indicates that the specific enhances DTH response is only achieved when a specific dose of cyclophosphamide is administered at a specific time, in combination with a proper priming dose.

The claims are drawn to a broad range of possible dosages, administration with or without CY, including numerous dosage variants and administration time variants of such, any number of or absence of adjuvants, etc. The claims (and the specification) do not even mention the induction dose, cited by applicant as critical for the alleged unexpected results. Thus claims drawn to any and all weekly administrations of the vaccine and variant administrations of the cyclophosphamide are not commensurate in scope with the alleged unexpected results. Further, that the weekly administration of a vaccine produces an equal or stronger immune response to an immunogen would not be unexpected, because the dose frequency is greater. Applicant cites the

decreased CY administration as presenting a critical difference which produces unexpected results. It is noted that this is not instantly claimed.

Therefor the as set forth above, it would have been prima facie obvious to modify the vaccine protocol taught in Berd et al. by administering weekly injections and one would have been motivated to do so for optimization of vaccine protocol. Further, the results achieved are not unexpected because the unexpected results described in the declaration by Dr. Berd and in the post filing evidence were neither disclosed in the instant specification, nor commensurate in scope with the instant claims.

Moving to address the product claims, applicant's arguments rely on an intended use to impart patentability to a product (weekly vs. Q28 day administration of a product), but intended use does not impart patentable weight to a product. See MPEP 2111.03:

Intended use recitations and other types of functional language cannot be entirely disregarded. However, in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey, 370 F.2d 576. 152 USPQ 235 (CCPA 1967); In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963)

See also In re Haller 73 USPQ 403 (CCPA 1947), where it is held that intended use, or application of printed matter to old article cannot render the article patentable. In the opinion text of In re Haller, it is stated that: Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is

concerned...In accordance with the patent statutes, an article or composition of matter, in order to patentable, must not only be useful and involve invention, but must also be *new*. If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition, regardless of the use for which it is intended. The difficulty is not that there can never be invention in discovering a new process involving the use of an old article, but that the statues make no provision for patenting of an article or composition which is not, in and of itself, new.

The product of Berd US Patent 5,290,551 is identical to the product instant claimed.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

August 13, 2001

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